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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/853,731	05/11/2001	Apollon Papadimitriou	20619	6504

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EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 08/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/853,731	PAPADIMITRIOU, APOLLON	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,25,27-34,38-42,51-55,59-61,67,68,71-77 and 83-108* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,25,27-34,38-42,51-55,59-61,67,68,71-77 and 83-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

Status of the Claims

2. Claims 24, 25, 27-34, 38-42, 51-55, 59-61, 67, 68, 71-77 and 83-108 are pending.

Applicants' amendment filed on June 9, 2005 is acknowledged. Applicants' response has been fully considered. Claims 24, 25, 27, 28, 34, 38, 39, 41, 51, 53, 54, 59-61, 67, 71, 73, 75 and 77 have been amended, claims 23, 26, 35 and 69-70 have been cancelled, and new claims 90-108 have been added. Thus, claims 24, 25, 27-34, 38-42, 51-55, 59-61, 67, 68, 71-77 and 83-108 are examined.

Withdrawn Claim Objection

3. The previous objection of claims 26-35, 38-42, 51-55, 59-61 and 77 is withdrawn in view of applicant's amendment to the claims, applicant's cancellation of the claim, and applicant's response at page 18 of the amendment filed June 9, 2005.

Withdrawn Claim Rejections-Obviousness Type Double Patenting

4. The previous rejection of claims 69 and 70 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of U. S. Patent 6,583,272, is withdrawn in view of applicant's cancellation of the claim in the amendment filed June 9, 2005.

5. The previous rejection of claims 69 and 70 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of copending

Application No. 10/014,363, is withdrawn in view of applicant's cancellation of the claim in the amendment filed June 9, 2005.

6. The previous rejection of claims 23, 26, 35 and 69-70 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-59 of copending Application No. 10/780,297 (US 2004/0147431), is withdrawn in view of applicant's cancellation of the claim in the amendment filed June 9, 2005.

Withdrawn Claim Rejections - 35 USC § 112

7. The previous rejection of claims 35 and 61 under 35 U.S.C. 112, second paragraph, as being indefinite, is withdrawn in view of applicant's amendment to the claims, applicant's cancellation of the claim, and applicant's response at pages 21-22 of the amendment filed June 9, 2005.

Withdrawn Claim Rejections - 35 USC § 102

8. The previous rejection of claims 23-25 under 35 U.S.C. 102(e) as anticipated by Burg *et al.* (U. S. Patent 6,340,742), is withdrawn in view of applicant's amendment to the claims, applicant's cancellation of the claim, and applicant's response at page 22 of the amendment filed June 9, 2005.

Maintained Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 83, 84, 88 and 89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 83, 84, 88 and 89 are indefinite as to a composition containing an EPO product, arginine and sodium sulfate with a pH 6 to 6.5 or pH 6.2, since arginine has a pKa of 1.8, 9 and 12.5, and H_2SO_4 is a strong acid, it is not clear how the composition can have a pH about 6-6.5 without a buffer reagent having a pKa in the range of pH 5 to 7.5.

Response to Arguments

Applicants indicate arginine/Na_2SO_4 is a buffer system to which an acid such as sulfuric acid is added as needed depending on the other components of the composition, to adjust the ultimate pH, and the arginine sulfate is prepared by weighing and solubilizing the indicated quantity of arginine and adjusting the pH to about 6-6.5 by titrating with sulfuric acid. Compositions using this buffer system and having the claimed pH are exemplified in paragraphs (0086) through (0088) and (0155) (page 22 of the response).

Applicants' response has been fully considered, however, the argument is not found persuasive because there is no functional group in the arginine/Na_2SO_4 having a pKa in the range of 6.0 to 6.5, which is required for preparing a stable buffer solution. The solution of arginine sulfate may be prepared as indicated in the specification, however, the pH of the solution is not going to be stable. A search in the literature fails to produce any reference citing arginine sulfate as a buffer for pH 6.0-6.5.

Claim Rejections-Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Previous rejection of claims 67-68, 71, 73, 75, 77, 83, 85 and 86 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of U. S. Patent 6,583,272 is maintained, and claims 91-101 and 104 have been added. Applicant's arguments have been fully considered, and the response to the argument is shown below.

Although the conflicting claims of the instant application and the patent are not identical, they are not patentably distinct from each other because claims 67-68, 71, 73, 75, 77, 83, 85, 86, 91-101 and 104 in the instant application disclose a liquid pharmaceutical composition comprising a pegylated EPO having the formula P-(NHCO-$(CH_2)_x$-$(OCH_2CH_2)_m$-OR)$_n$, a multiple charged inorganic anion and a buffer at pH 5.5-7.0, optionally having other ingredients such as NaCl, mannitol and arginine, wherein P is EPO having the sequence of SEQ ID NO:1 or 2, or, the sequence modified by the addition of 1-6 glycosylation sites or rearrangement of at least one glycosylation site, minus the n amino group of the EPO. This is an obvious variation in view of claims 1-13 in the patent which disclose a conjugate comprising an EPO glycoprotein having N-terminal α-amino group and one poly(ethyleneglycol), wherein EPO has the sequence of SEQ ID NO:1, and EPO is linked to –CO-$(CH_2)_x$-$(OCH_2CH_2)_m$-OR via an amide bond; and the specification of the patent discloses the peg-EPO product can be prepared in various formulations containing a multiple charged inorganic anion and a buffer at pH 5.5-7.0, optionally having other ingredients such as NaCl, mannitol and arginine, e.g., a formulation having 10 mM

phosphate, 40 mM sulfate, 4% mannitol, pH 6.2 (Examples 6 and 8; Table 3; Fig. 4). In view of the teachings in the specification of the patent, it is obvious that the claimed peg-EPO conjugate can be prepared as a pharmaceutical formulation comprising a multiple charged inorganic anion such as sulfate and a buffer such as phosphate at pH 5.5-7.0 as the claimed composition in the instant application. Thus, claims 67-68, 71, 73, 75, 77, 83, 85, 86, 91-101 and 104 in present application and claims 1-13 in the patent are obvious variations of a pharmaceutical composition comprising a peg-EPO conjugate, a multiple charged inorganic anion such as sulfate and a buffer such as phosphate at pH 5.5-7.0.

Response to Arguments

Applicants indicate the PTO recognizes that the claims of the patent 6,583,272 do not support this rejection, so the PTO has to rely upon the specification and examples of the patent. However, the PTO cannot use the teaching of the specification of the '272 patent in support of this rejection. In addition, the '272 patent does not claim a pharmaceutical composition, it claims a pegylated erythropoietin glycoprotein. While the stated utility of the glycoprotein of the '272 patent is as a pharmaceutical product, that does not mean that the issued claims are directed to a pharmaceutical composition or that they necessarily obviate every formulation that may include an erythropoietin product (pages 19-20 of the response).

Applicants' response has been fully considered, however, the argument is not found persuasive because the specification discloses the pharmaceutical composition comprises the claimed pegylated erythropoietin and other ingredients such as sulfate, phosphate and NaCl. Furthermore, the stated utility of glycoprotein of the '272 patent is as a pharmaceutical product. Thus, it is obvious that the claimed erythropoietin product of the patent would be prepared as a

pharmaceutical composition comprising other components cited in the specification, and the rejection is maintained.

11. Previous rejection of claims 67-68 and 71-77 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of U. S. Patent copending Application No. 10/014,363 is maintained, and claims 91-108 have been added. Applicant's arguments have been fully considered, and the response to the argument is shown below.

Although the conflicting claims of the instant application and the copending application are not identical, they are not patentably distinct from each other because claims 67-68, 71-77 and 91-108 in the instant application disclose a liquid pharmaceutical composition comprising a pegylated EPO such as EPO linked to $-CO-(CH_2)_x-(OCH_2CH_2)_m-OR$ via an amide bond, a multiple charged inorganic anion, and a buffer at pH 5.5 to 7.0, optionally having other ingredients such as NaCl, methionine, mannitol and pluronic F68. This is an obvious variation in view of claims 1-16 in the copending application which disclose a conjugate comprising an EPO glycoprotein having N-terminal α-amino group and one poly(ethyleneglycol), where EPO is linked to $-CO-(CH_2)_x-(OCH_2CH_2)_m-OR$ via an amide bond, and a pharmaceutical composition comprising the conjugate; and the specification of the copending application discloses the peg-EPO product (e.g., 10 to 10,000 μg/ml) can be prepared in various compositions containing a multiple charged inorganic anion (e.g., 10-200 mmole/l sulfate) and a buffer (e.g., 10 to 50 mmol/l phosphate) at pH 5.5-7.0, optionally having other ingredients such as NaCl, mannitol, methionine and pluronic F68 (paragraphs [0068]-[0072]). In view of the teachings in the specification of the copending application, it is obvious that the claimed pharmaceutical

composition can be prepared as a composition comprising the peg-EPO conjugate and additionally, a multiple charged inorganic anion such as sulfate, a buffer such as phosphate, and other ingredients at pH 5.5-7.0 as the claimed composition in the instant application. Thus, claims 67-68, 71-77 and 91-108 in present application and claims 1-16 in the copending application are obvious variations of a pharmaceutical composition comprising a peg-EPO conjugate, a multiple charged inorganic anion, a buffer and other ingredients at pH 5.5-7.0.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicants indicate claims 1-15 of co-pending USSN 10/014,363 are directed to an erythropoietin glycoprotein conjugate, not a pharmaceutical formulation, and claim 16 of USSN 10/014,363 is directed to a pharmaceutical composition, it does not provide for the foregoing formulation components in instant claims 67-76. Alternatively, as applicant does not know what claims, if any, may ultimately issue in either the instant application or in USSN 10/014,363, and thus cannot fairly now assess the extent to which there may be any overlap, applicant requests that this provisional election be held in abeyance until there is an indication of allowable claims in either application, at which time applicant can properly assess the propriety of filing a terminal disclaimer (page 20 of the response).

Applicants' response has been fully considered, however, the argument is not found persuasive because claim 16 of USSN 10/014,363 is directed to a pharmaceutical composition, although the claim does not recites the foregoing formulation components of the claims in the instant application, the specification discloses the formulation components and the amounts of

the components in the pharmaceutical compositions (see paragraphs [0068]-[0072]), it is obvious that the claimed pharmaceutical composition can be prepared as a composition comprising the formulation components as the claimed composition in the instant application. Since the terminal disclaimer is not filed, the rejection is maintained.

12. Previous rejection of claims 24, 25, 27-34, 38-42, 51-55, 59-61, 67, 68, 71-77 and 83-89 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16, 18, 22-37 and 39-68 of U. S. Patent copending Application No. 10/780,297 (US 2004/0147431; allowable claims) is maintained, and claims 90-108 have been added. Applicant's arguments have been fully considered, and the response to the argument is shown below.

Although the conflicting claims of the instant application and the copending application are not identical, they are not patentably distinct from each other because claims 24, 25, 27-34, 38-42, 51-55, 59-61, 67, 68, 71-77 and 83-108 in the instant application disclose a liquid pharmaceutical composition comprising a pegylated EPO, a multiple charged inorganic anion, a buffer at pH of 5.5 to 7.0, optionally with other ingredients such as NaCl, mannitol and methionine; and a liquid pharmaceutical composition comprises an EPO product, a specific multiple charged inorganic anion, a buffer and other ingredients at pH 6 to 6.5, optionally with other ingredients. This is an obvious variation in view of claims 1-16, 18, 22-37 and 39-68 in the copending application which disclose a liquid pharmaceutical composition consisting essentially of an EPO glycoprotein product or a pegylated EPO, a multiple charged inorganic anion, a buffer and a methionine at pH of 5.5 to 7.0, optionally with other ingredients such as NaCl and mannitol. Both the claims of the instant application and the claims of the copending application

are directed to a pharmaceutical composition comprising an EPO glycoprotein product or a pegylated EPO, a multiple charged inorganic anion and a buffer at pH of 5.5 to 7.0. Claims 23-35, 38-42, 51-55, 59-61, 67-77 and 83-108 in present application and claims 1-16, 18, 22-37 and 39-68 in the copending application are obvious variations of a pharmaceutical composition comprising an EPO glycoprotein product, a multiple charged inorganic anion, methione and a buffer at pH of 5.5 to 7.0, optionally with other ingredients such as NaCl and mannitol.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicants indicate the 10/780,297 application (a child case of instant application) claims pharmaceutical compositions containing any of a number of erythropoietins, all of which formulations also include methionine as an antioxidant and are stable at room temperature for a certain period of time. Applicant submits the claims of '297 application and those of the instant application are thus patentably distinct. Alternatively, as applicant does not know what claims, if any, may ultimately issue in either the instant application or in US Serial No. 10/780,297, and thus can not fairly assess now the extent to which there may be any overlap, applicant requests that this provisional election be held in abeyance until there is an indication of allowable claims in either application, at which time applicant can properly assess the propriety of filing a terminal disclaimer (page 21 of the response).

Applicants' response has been fully considered, however, the argument is not found persuasive because the claims of 10/780,297 are directed to a pharmaceutical composition comprising an erythropoietin product, a multiple charged inorganic anion, a buffer and

methionine at pH of 5.5 to 7.0, optionally with other ingredients such as NaCl and mannitol, in which the scope of the claims is overlapped with the claims of the instant application as indicated above. Since the terminal disclaimer is not filed, the rejection is maintained.

Reinstated Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 67-68, 71, 73, 75, 77, 83, 85, 86, 91-101 and 104 are rejected under 35 U.S.C. 102(e) as being anticipated by Bailon (U.S. Patent 6,583,272 B1, priority date July 2, 1999).

Bailon teaches a conjugate of erythropoietin (EPO) with poly(ethylene glycol) (PEG) and a pharmaceutical composition comprising therapeutically effective amount of the conjugate for administering to patients (column 3, lines 23-46), wherein the conjugate comprises an EPO such as human EPO and analogs having at least one free amino group and having in vivo biological activity. The EPO conjugate can be represented by formula (I), P-[NHCO-$(CH_2)_x$-$(OCH_2CH_2)_m$-OR]$_n$, wherein R is lower alkyl, x is 2 or 3, m is 450-900, n is 1-3, n and m are such that the molecular weight of the conjugate minus the EPO is from 20 to 100 kDa (column 1, line 64-column 3, line 6; column 3, line 48-column 4, line 31) and the EPO including both naturally or recombinantly produced human erythropoietin having the amino acid sequence of SEQ ID NO:1 or 2 can be modified as analogs having 1-6 additional glycosylation sites or a rearrangement of at

least one site for glycosylation, for example, the conjugate such as mono-PEG-EPO or di-PEG-EPO is prepared in a phosphate buffer, pH 7.5 with a 30 kDa methoxy PEG-SBA reagent (Examples 2, 5), and a pegylated EPO (10-400 μg/ml, Table 3; 0.6-1.2 mg/ml, Example 6) is formulated in a sulfate-containing buffer at pH 6.2, e.g., 10 mM phosphate, 140 mM sulfate, pH 6.2; 10 mM (corresponding to 1.38 mg/ml) phosphate, 40 mM (corresponding to 5.67 mg/ml) sulfate, 4% mannitol, pH 6.2; 50 mM arginine, 100 mM sulfate, pH 6.2 and these pegylated EPO in various formulations are stable at room temperature (Fig. 4; Example 8, Table 3; claims 67, 68, 71, 73, 75, 77, 83, 85, 86, 91-101 and 104).

The previous rejection of claims 1-17, 19, 26-42, 44, 51, 59 and 67-70 under 35 U.S.C. 102(e) as being anticipated by Bailon (U.S. Patent 6,583,272 B1) has been withdrawn in the Office Action dated May 12, 2004. Upon reconsideration, it is found that Declaration of Dr. Appollon Papadimitriou filed under 37 CFR 1.132 is not suitable for the withdrawal of the 102(e) rejection, since Dr. Appollon Papadimitriou is not an inventor of U. S. Patent 6,583,272, which has disclosed the pharmaceutical composition comprising the PEG-EPO.

Conclusion

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CHIH-MIN KAM
PATENT EXAMINER

CMK
July 27, 2005